

REMARKS

The applicants thankfully acknowledges the withdrawal of the previous rejections under §112, second paragraph, and §103(a).

Claims 20-29 are pending in the instant application. No new matter is introduced by this Preliminary Amendment. Support for the amendment to Claim 20 is found on page 40 of the specification. Support for the amendment to Claim 22 is found at page 22 of the specification. Support for new Claim 29 is found at page 50.

1. Claim 19 stands objected to under 37 CFR 1.75(c) as being in improper form because it is a multiple dependent claim dependent on subsequent Claim 20.

Withdrawal of this rejection is requested as claim 19 has been canceled.

2. Claims 19-28 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 19 is indefinite because it is unclear as to what is encompassed within the term “processor.”

Withdrawal of this rejection is requested as claim 19 has been canceled and new claim 29 specifically defines what is encompassed by the term “processor.”

B. Claim 22 is vague and indefinite in the use of the conductive oligomer formula.

a. The intended composition of B has not been outlined.

b. D is not defined when $g = 1$.

c. The word “preferably” is unclear in this context

Withdrawal of this rejection is requested as claim 22 has been amended.

3. Applicants acknowledge the Examiner’s argument that the listing of references in the specification is not a proper information disclosure statement, and that the references have not been considered. The listing of references in the specification is not intended by applicants to be an information disclosure statement, rather the listing merely expands and enhances the teaching of the specification. A proper information disclosure statement and proper subsequent supplemental information disclosure statements have been filed in connection with the instant application. Accordingly, Applicants respectfully request withdrawal of the rejection relating to the listing of these references in the specification.

4. The specification has been checked for minor errors and corrected where necessary. Accordingly, Applicants respectfully request withdrawal of the rejection.

5. Trademarks have been capitalized wherever they appear and are accompanied by the appropriate generic terminology. Accordingly, withdrawal of the rejection is requested.

6. The Applicants acknowledge Examiner’s argument that the chemical structures appearing on pages 14-20 and 22-33 should be submitted to the office as required by 37 CFR 1.81, but respectfully disagrees. Applicants point to 37 CFR 1.58(a) which states, “[t]he specification, including the claims, may contain chemical and mathematical formulas....” Applicants submit

that the chemical structures in question are, chemical formulas allowable under 37 CFR 1.58(a).

In support of their position, Applicants have enclosed United States Patent No. 6,013,170 (attached hereto as Exhibit A) and exemplary pages from allowed Application Serial No. 08/911,589 (attached hereto as Exhibit B) which contain chemical formulas similar to those found in the present application. Accordingly, Applicants request withdrawal of this rejection.

7. Claims 18-28 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-36 of US Patent No. 6,096,273.

Withdrawal of this rejection is requested as an appropriate terminal disclaimer is filed herewith.

8. Claims 18-28 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 19-40 of co-pending Application No. 08/873,597.

Withdrawal of this rejection is requested as an appropriate terminal disclaimer is filed herewith.

9. 35 U.S.C. 103(a) rejections:

A. Claims 18-22 stand provisionally rejected under 35 U.S.C. 103(a) as being obvious over co-pending Application No. 08/873,597 and US Patent No. 6,096,273.

While the Examiner has indicated that the claims are rejected under 35 U.S.C. 103(a), Applicants note that as a result of the present filing of a continuing application under 37 C.F.R. 1.53(d), the present application is subject to the new rules for applications filed subsequent to

November 29, 1999. As such, Applicants submit that copending Application No. 08/873,597 and US Patent No. 6,096,273 are not prior art against the present application. That is, revised 35 U.S.C. 103(c) provides that “[s]ubject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f), and (g) of section 102...shall not preclude patentability under this section where the subject matter and the claimed invention were...subject to an obligation of assignment to the same person.”

The 6,096,273 patent issued August 1, 2000 and has a filing date of November 5, 1996. The present application was filed June 12, 1998. As such, the present application was filed prior to the issuance of the 6,096,273 patent, but subsequent to the filing of the 6,096,273 patent, a potential 102(e) situation. However, Applicants submit that the 6,096,273 patent and the present application are assigned to the same entity, namely Clinical Micro Sensors, Inc. In support of this, Applicants are submitting copies of the assignment of the present application and a copy of the front page of the 6,096,273 patent which indicates that Clinical Micro Sensors, Inc. is the assignee. In addition, Applicants draw the Examiner’s attention to reel/frame 8757/0001 which documents the assignment of the 6,096,273. In addition, Applicants respectfully direct the Examiner to reel/frame 9555/0326 which documents the assignment of the present case. Since both the present application and the 6,096,273 patent were subject to an obligation of assignment at the time the present invention was made, Applicants submit that the 6,096,273 patent is not a proper reference upon which to base a rejection under 103(a). Accordingly, Applicants respectfully request the Examiner to withdraw this rejection as to the 6,096,273 patent.

The 08/873,597 application has a filing date of June 12, 1997. As stated above, the present application was filed June 12, 1998. As such, the present application was filed

subsequent to the filing of the 08/873,597 application, a potential 102(e) situation. However, Applicants submit that the 08/873,597 application and the present application are assigned to the same entity, namely Clinical Micro Sensors, Inc. In support of this, Applicants are submitting copies of the assignments of the two applications which indicate that Clinical Micro Sensors, Inc. is the assignee. In addition, Applicants draw the Examiner's attention to reel/frame 8875/0764 which documents the assignment of application No. 08/873,597. Furthermore, Applicants respectfully direct the Examiner to reel/frame 9555/0326 which documents the assignment of the present case. Since both the present application and the 08/873,597 application were subject to an obligation of assignment at the time the present invention was made, Applicants submit that the 08/873,597 application is not a proper reference upon which to base a rejection under 103(a). Accordingly, Applicants respectfully request the Examiner to withdraw this rejection as to the 08/873,597 application.

B. Claims 18, 19, 21 and 24-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keen (US Patent No. 6,060,327) in view of Kossovsky et al. (US Patent No. 5,585,646).

As discussed in response to the November 22, 1999 Office Action, the present invention is directed to the detection of analytes using a biosensor. Detection in this system is based on the fact that at least one redox property of a redox active molecule is altered as a result of its association with a target analyte. The change in the redox property of the redox active molecule as a result of association with an analyte alters the faradaic impedance of the system. This alteration in the faradaic impedance of the system results in a detectable signal.

Thus, the present invention provides a biosensor for the detection of target analytes. The biosensor comprises electrodes, a self-assembled monolayer and a binding ligand covalently attached to an electrode(s) via a spacer, such as a conductive oligomer.

Keen is directed to a sensor comprised of three functional aspects. First, it has a plurality of conductive polymer strands, such as nucleic acid, each having a first and second end, aligned in a common orientation. Second, it has a plurality of head groups that are attached to the first end of the conductive polymer strands, each head group capable of an enzymatic reaction resulting in the generation of electrons. Third, it has an electrode substrate attached to the second end of the conductive polymer strands.

As acknowledged by the Examiner, the Keen reference does not disclose self-assembled monolayers.

Kossovsky et. al., describe bioelectronic devices in which a layer of electronically active biochemical material is bound to the surface of a semiconductor substrate via a stabilization layer comprising an oligomer. First of all, there is no evidence in Kossovsky that this oligomer forms a “self-assembled monolayer” as is known in the art. Secondly, this oligomer is coated on the semiconductor, not covalently bound as required in the present invention. Thirdly, the biochemical layer is also non-covalently bound to the oligomer. Kossovsky et al. teach that modification in surfaces of semiconductors can impact their electrical performance. However, neither the teachings of Kossovsky or references cited within disclose the use of semiconductors as biosensors for the detection of analytes in biological samples. That is, there is no detection of target analytes, no SAM, no binding ligand, and no arrays in Kossovsky, as acknowledged by the Examiner at page 3 of the present office action.

To establish a *prima facie* case of obviousness three criteria must be met: i) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; ii) there must be a reasonable expectation of success; and iii) the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) M.P.E.P. §2143.

As a preliminary matter, Applicants reassert their arguments that Kossovsky is not analogous art as modifying the surface of semiconductors is not in the field of applicant's endeavor, nor reasonably pertinent to the development of biosensors capable of detecting specific substances. (See *In re Oetiker*, 977 F.2d 1443, 1446, 24 U.S.P.Q.2d 1443, 1445 (Fed.Cir. 1992); MPEP §2141.01(a); "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned."). In support of this position of non-analogous art, the Applicants draw the Examiner's attention to M.P.E.P. § 2141.01(a), which outlines the guidelines regarding analogous art. The present invention has been placed in class 422, Chemical Apparatus and Method, while Kossovsky is in class 257, "Active Solid State Devices" (e.g. Transistors and Solid-State Diodes). Therefore the requirement that there be some suggestion or motivation to modify or combine the references has not been met, and the rejection should be withdrawn.

Even assuming, *arguendo*, that motivation to combine exists, there is no reasonable

expectation of success. The invention disclosed by Kossovsky is directed toward a method of coating semi-conductors with films to prevent or reduce deactivation of electronically active biochemical molecules bound to semiconductor surfaces present in a solid state electronic device. Thus, Kossovsky cannot provide a reasonable expectation of success.

Finally, the Examiner has acknowledged that neither Keen nor Kossovsky disclose self-assembled monolayers, therefore the requirement that the prior art references teach or suggest all the claim limitations is not met.

Thus, Applicants respectfully assert that Keen and Kossovsky either alone or in combination, do not support a conclusion of obviousness. Applicants respectfully request the rejection be withdrawn.

C. Claims 20-21 and 24-28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Keen (US Patent No. 6,060,327) in view of Wohlstadter et al. (US Patent No. 6,090,545).

Keen (U.S. Patent No. 6,060,327) is discussed above.

Wohlstadter et al. disclose materials and methods for producing patterned multi-array, multi-specific, "PMAMS", surfaces which are electronically excited for use in electrochemiluminescence based tests. The PMAMS comprises a plurality of binding domains deposited on a surface and spatially aligned with one or more electrodes and one or more counterelectrode pairs for exciting electrochemiluminescent labels to create light, which is then detected.

As discussed above, to establish a *prima facie* case of obviousness there must be: i) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, ii) there must be a reasonable expectation of success; and, iii) the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) M.P.E.P. §2143.

Applicants assert that there is no motivation to combine these two references. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990) M.P.E.P. §2143.01. The possibility that a combination may increase economic efficiency is not sufficient to prove the prior art suggested the desirability of the combination.

Secondly, there is no reasonable expectation of success. Wohlstadter relies on electrochemiluminescent detection, not electronic detection for the detection of target analytes. Keen relies on the GOD active site/redox center of the FAD/FADH₂ to provide an electron transfer pathway to the surface of a conductive surface upon binding of a target analyte. As argued above, the sensor taught by Keen lacks self-assembled monolayers which are important in the present invention for preventing electrical contact between the electrodes and the electron transfer moieties, or between the electrode and charged species within the solvent.

Given the teachings of Wohlstadter and Keen, the reasonably skilled artisan would not have a reasonable expectation of success in arriving at the instant invention given the cited

references and knowledge available in the art at the time of filing.

Furthermore, the references cited do not teach or suggest all of the claim limitations. Wohlstadter relies on electrochemiluminescence and does not disclose the use of an electronic detector. Keen relies on the GOD active site/redox center of the FAD/FADH₂ to provide an electron transfer pathway to the surface of a conductive surface upon binding of a target analyte. The instant application requires electronic detection of the signal. Therefore, the requirement that the prior art references teach or suggest all the claim limitations is not met.

Thus, Applicants respectfully assert that Keen and Wohlstadter either alone or in combination, do not support a conclusion of obviousness. Applicants respectfully request the rejection be withdrawn.

D. Claims 22 and 23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Keen (US Patent No. 6,060,327) in view of Kossovsky et al. (US Patent No. 5,585,646) further in view of Meade (US Patent No. 6,013,459).

Please see the previous discussion of Keen and Kossovsky above.

While the Examiner has indicated that the claims are rejected under 35 USC 103(a), Applicants note that as a result of the present filing of a continuing application under 37 C.F.R. 1.53(d), the present application is subject to the new rules for applications filed subsequent to November 29, 1999. As such, Applicants submit that Meade is not prior art against the present application. That is, revised 35 U.S.C. 103(c) provides that “[s]ubject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f), and (g) of section 102...shall not preclude patentability under this section where the subject matter and the

claimed invention were...subject to an obligation of assignment to the same person.”

Applicants submit that Meade and the present application are assigned to the same entity, namely Clinical Micro Sensors, Inc. In support of this, Applicants are submitting copies of the assignments of the two applications which indicate that Clinical Micro Sensors, Inc. is the assignee, attached hereto as Exhibits C and D. Applicants draw the Examiner’s attention to reel/frame 9555/0167 (Exhibit C) which documents the assignment of the Meade reference. Furthermore, Applicants respectfully direct the Examiner to reel/frame 9555/0326 (Exhibit D) which documents the assignment of the present case. As Meade is not an appropriate reference under 35 USC 103(a), Applicants respectfully request withdrawal of this rejection

E. Claims 22 and 23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Keen (US Patent No. 6,060,327) in view of Wohlstadter et al. (US Patent No. 6,090,545) and further in view of Meade (US Patent No. 6,013,459).

Please see the discussion of Keen and Wohlstadter above.

Please see the discussion of Meade above.

As Meade is not an appropriate reference under 35 USC 103(a), Applicants respectfully request withdrawal of this rejection.

Attached hereto is a marked-up version of the changes made to the claims by the “Restriction and Amendment”. The attached page is captioned **“Version with markings to show changes made.”**

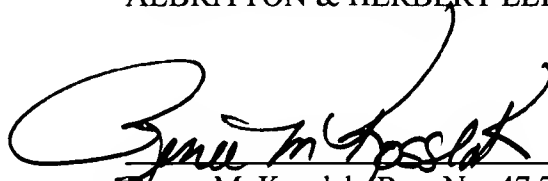
Applicants respectfully submit that the Claims are now in condition for allowance and

early notification to that effect is respectfully requested. If after review, the Examiner feels there are further unresolved issues, the Examiner is invited to call the undersigned at (415)781-1989.

Dated: 4/3/01

Respectfully submitted,

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“VERSION WITH MARKINGS TO SHOW CHANGES MADE”

In the specification:

The paragraph beginning at page 2, line 15, has been amended as follows:

[Accordingly] [I]n accordance with the above objects, the present invention provides methods of detecting a target analyte in a test sample comprising a redox active molecule and an analyte. The method comprises applying an input signal to the test sample and detecting a change in the faradaic impedance of the system as a result of the association of the redox active molecule with the analyte.

The paragraph beginning at page 26, line 26, has been amended as follow:

As will be appreciated by those in the art, a large number of possible conductive oligomers may be utilized. These include conductive oligomers falling within the Structure 1 and Structure 8 formulas, as well as other conductive oligomers, as are generally known in the art, including for example, compounds comprising fused aromatic rings or [Teflon®] TEFLON® (polytetrafluoroethylene)-like oligomers, such as $-(CF_2)_n-$, $-(CHF)_n-$ and $-(CFR)_n-$. See for example, Schumm et al., *angew. Chem. Intl. Ed. Engl.* 33:1361 (1994); Grosshenny et al., *Platinum Metals Rev.* 40(1):26-35 (1996); Tour, *Chem. Rev.* 96:537-553 (1996); Hsung et al., *Organometallics* 14:4808-4815 (1995; and references cited therein, all of which are expressly incorporated by reference.

In the claims:

Claim 19 has been cancelled.

Claim 20 has been amended as follows:

20. (Amended) An apparatus for the detection of a non-nucleic acid target analyte in a test sample, comprising:

a) a test chamber comprising an array of electrodes each comprising:

i) a self-assembled monolayer; and

ii) a binding ligand covalently attached to said electrode via a spacer;

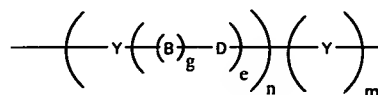
wherein said test chamber further comprises at least one second measuring electrode; and

b) a voltage source electrically connected to said test chamber[.] ; and

c) an electronic detector.

Claim 22 has been amended as follows:

22. (Amended) An apparatus according to claim 21 wherein said conductive oligomer has the formula:



wherein

Y is an aromatic group;

n is an integer from 1 to 50;

g is either 1 or zero;

e is an integer from zero to 10; and

m is zero or 1;

wherein when g is 1, B-D is selected from acetylene, alkene, substituted alkene, amide, azo, esters, thioesters, -CH=N-, -CR=N-, -N=CH- and -N=CR-, -SiH=SiH-, -SiR=SiH-, -SiR=SiH-, and -SiR=SiR-, -SiH=CH-, -SiR=CH-, -SiH=CR-, -SiR=CR-, -CH=SiH-, -CR=SiH-, -CH=SiR-, and -CR=SiR-; and

and

wherein when g is zero, e is 1 and D is [preferably] carbonyl, or a heteroatom moiety, wherein the heteroatom is selected from oxygen, sulfur, nitrogen, silicon or phosphorus.

New Claim 29 has been added.

29. (New) An apparatus according to claim 20 further comprising a processor for data analysis.

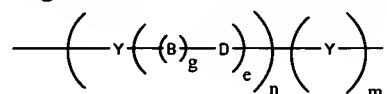
Appendix of Pending Claims

20. (Amended) An apparatus for the detection of a non-nucleic acid target analyte in a test sample, comprising:

- a) a test chamber comprising an array of electrodes each comprising:
 - i) a self-assembled monolayer; and
 - ii) a binding ligand covalently attached to said electrode via a spacer;
 wherein said test chamber further comprises at least one second measuring electrode; and
- b) a voltage source electrically connected to said test chamber; and
- c) an electronic detector.

21. (Amended) An apparatus according to claim 20 wherein said spacer is a conductive oligomer:

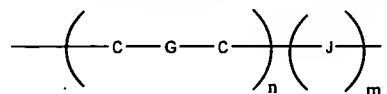
22. (Amended) An apparatus according to claim 21 wherein said conductive oligomer has the formula:



wherein

- Y is an aromatic group;
 - n is an integer from 1 to 50;
 - g is either 1 or zero;
 - e is an integer from zero to 10; and
 - m is zero or 1;
- wherein when g is 1, B-D is selected from acetylene, alkene, substituted alkene, amide, azo, esters, thioesters, -CH=N-, -CR=N-, -N=CH- and -N=CR-, -SiH=SiH-, -SiR=SiH-, -SiR=SiH-, and -SiR=SiR-, -SiH=CH-, -SiR=CH-, -SiH=CR-, -SiR=CR-, -CH=SiH-, -CR=SiH-, -CH=SiR-, and -CR=SiR-; and
- wherein when g is zero, e is 1 and D is [preferably] carbonyl, or a heteroatom moiety, wherein the heteroatom is selected from oxygen, sulfur, nitrogen, silicon or phosphorus.

23. An apparatus according to claim 21 wherein said conductive oligomer has the formula:



wherein

- n is an integer from 1 to 50;
- m is 0 or 1;
- C is carbon;
- J is carbonyl or a heteroatom moiety, wherein the heteroatom is selected from the group consisting of oxygen, nitrogen, silicon, phosphorus, sulfur; and
- G is a bond selected from alkane, alkene or acetylene, wherein if m = 0, at least one G is not alkane.

24. (Amended) An apparatus according to claim 20 wherein said spacer is an insulator.

25. (Amended) An apparatus according to claim 20 wherein said self-assembled monolayer comprises insulators.

26. (Amended) An apparatus according to claim 20 wherein said self-assembled monolayer comprises

conductive oligomers.

27. (Amended) An apparatus according to claim 20 wherein said self-assembled monolayer comprises insulators and conductive oligomers.

28. (Amended) An apparatus according to claim 20 wherein said binding ligand is a protein.

29. (New) An apparatus according to claim 20 further comprising a processor coupled to said electrodes and configured to receive an output signal.